REMARKS/ARGUMENTS

Claims 1-13 and 16-22 were pending in this application. Claims 6, 16, and 21 have been amended. No claims have been added or canceled. Hence, claims 1-13 and 16-22 remain pending. Support for the amendments may be found at *e.g.*, see original claims 18, 21, specification at page 2, lines 26-30. Also, claims 6 and 21 have been amended to correct obvious typographical errors, and as such, these amendments do not narrow the scope of the claims in any regard. Entry of the present amendment, and reconsideration of the subject application as amended is respectfully requested.

Claims Rejected Under 35 U.S.C. 112, First Paragraph, Written Description

Claims 1-19 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in a manner that reasonably conveys to one of ordinary skill in the art that the inventors had possession of the claimed invention at the time of filing. This rejection is respectfully traversed for at least the reasons which follow.

The purpose of the written description requirement is simply to ensure that the inventors had possession of the claimed subject matter, *i.e.*, to ensure that the inventors actually invented what is claimed. *See Gentry Gallery Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479, 45 U.S.P.Q.2d 1498, 1503 (Fed. Cir. 1998); *Lockwood v. American Airlines*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997); *In re Alton*, 76 F.3d 1168, 1172, 37 U.S.P.Q.2d 1578, 1581 (Fed. Cir. 1996). In accordance with this purpose, Applicants need not "describe," in the sense of Section 112, all things that are encompassed by the claims. A related and equally well-established principle of patent law is that claims "may be broader than the specific embodiment disclosed in a specification." *Ralston Purina Co. v. Far-mor-Co*, 772 F.2d 1570, 1575, 227 U.S.P.Q. 177, 179 (Fed. Cir. 1985) (*quoting In re Rasmussen*, 650 F.2d 1212, 1215, 211 U.S.P.Q. 323, 326 (C.C.P.A. 1981)). Thus, 35 U.S.C. §112, first paragraph, does not require that Applicants reduce to practice or describe each and every C1 inhibitor falling within the scope of the claims through examples. To contend otherwise would contradict established jurisprudence, which teaches that a patent may be infringed by technology developed after a patent issues.

United States Steel Corp. v. Phillips Petroleum Co., 865 F.2d 1247, 1251, 9 U.S.P.Q.2d 1461, 1464 (Fed. Cir. 1989).

Further, "a description as filed is presumed to be adequate, unless and until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption." *Federal Register* 66(4):1107, Written Description Guidelines (2001). In this regard, the Examiner is required to disclose "express findings of fact which support the lack of written description conclusion." *Id.* However, in the present case, general statements such as an alleged "paucity in the art" are relied upon to support a finding of lack of written description. *Office Action* mailed April 19, 2006 at page 3. This contravenes stated Patent Office policy stipulating that "[a] general allegation of 'unpredictability in the art' is not sufficient reason to support a rejection for lack of adequate written description." (emphasis added) *Federal Register* 66(4) at 1107. Therefore, it is submitted that a *prima facie* case of insufficient written description has not been established.

Nonetheless, it is submitted that the present specification discloses the modification of glycosylated compounds generally by modification of O-linked carbohydrates to change plasma circulatory half-life, and claims C1 inhibitors as a preferred type of glycosylated compound. Based on such disclosure, one of skill would recognize the various known sources of unmodified C1 inhibitors as being within the scope of the presently claimed invention, with the exemplified rhC1INH as a particularly preferred recombinant C1 inhibitor source compound. However, one of skill would understand the inventors to be in possession of the claimed, broader class of all known unmodified C1 inhibitor compounds within the context of certain aspects of the generally disclosed invention, *e.g.*, modification of O-linked carbohydrates to modify plasma circulatory half-life of glycoproteins.

In this regard, what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 U.S.P.Q. at 94. As general sources of C1 inhibitor were known to those skilled in the art at the time of filing, Applicants did not need to disclose each and every known C1 inhibitor to comply with the written description requirement. Rather, Applicants provided express disclosure in the original claims of C1 inhibitors generally, and exemplified rhC1INH as a preferred

embodiment in the specification. Based on such disclosure, a skilled artisan would have understood the inventor to be in possession of the genus of modified C1 inhibitors generally at the time of filing, even if every nuance of every known source of C1 inhibitor was not explicitly described in the specification. See, *e.g.*, *M.P.E.P.* § 2163 at page 2100-180.

Moreover, in addition to the working examples involving rhC1INH, Applicants have disclosed general *in vitro* and *in vivo* methodologies, including methods and enzymes for capping or removal of terminal galactose residues, and sialylation,. (see, *e.g.*, US Pat 5,541,083, WO 98/31826, and the recited EC numbers of various enzymes on page 3 of the specification). Applicants have also provided disclosure of methodologies for removal of part or all of an O-linked carbohydrate chain *via in vitro* (*e.g.*, enzyme incubation) and *in vivo* (*e.g.*, enzyme co-expression). (See, *e.g.*, page 3-4 of the specification). Such disclosure clearly illustrates the inventors to be in possession of the claimed C1 inhibitors, as well as demonstrating means for achieving the claimed C1 inhibitors commensurate in scope with the claims. For at least this reason, it is respectfully submitted that the present claims meet the written description provision under 35 U.S.C. § 112, first paragraph.

In addition, whether the specification shows that Applicants were in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. See *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998).

In the present case, it is submitted that the disclosure of a limited number of the claimed C1 inhibitors with modified O-linked carbohydrates *via* the examples in combination with many additional factors, in fact does provide sufficient written description for the present claims. Such

factors include, *e.g.*, exemplary enzymes for the modification of O-linked carbohydrates and numerous methodologies to modify O-linked carbohydrates to thereby change plasma circulatory half-life, as well as methods to verify a change in plasma circulatory half-life. Therefore, it is clear that one of ordinary skill in the art would recognize that Applicants were in possession of the genus of claimed C1 inhibitors.

Accordingly, for at least the foregoing reasons, the rejection under 35 U.S.C. §112, first paragraph, written description, is traversed, and withdrawal of this rejection is respectfully requested.

Claims Rejected Under 35 U.S.C. 112, First Paragraph, Enablement

Claims 16-22 stand rejected under 35 U.S.C. §112, first paragraph, enablement, as allegedly not enabling any person skilled in the art to make and use the invention commensurate in scope with the claims. This rejection is respectfully traversed for at least the reasons which follow.

While not agreeing with the Office Action's characterizations, claim 16 has been amended to clarify that the method relates to a method for extending the blood circulatory half-life of a glycoprotein or glycoprotein comprising compound, wherein the method includes, in certain aspects, modification of glycoprotein compounds *via* non-human transgenic animals. Thus, the claims do not relate to any alleged "gene therapy" of humans. Rather, the claims relate to the discovery, in accordance with certain aspects of the presently claimed invention, of a method for extending blood circulatory half-life by removal of one or more non-sialylated O-linked carbohydrate from a glycoprotein. In accordance with the present method claims, the *in vivo* aspects of the methods relate to co-expression in cells or non-human transgenic animals. As such, the Examiner's concerns regarding gene therapy of humans is moot. For at least this reason, withdrawal of this rejection is respectfully requested.

In any event, the first paragraph of section 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains...to make and use the same". Applicants, through detailed, objective guidance and examples teach the manner and process of making and using the invention in terms commensurate in scope with the claims.

"Under these circumstances, the specification is presumptively sufficient; it must be taken as... [enabling] unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support". *In re Marzocchi & Horton*, 169 U.S.P.Q. 367,369 (C.C.P.A. 1971) (emphasis in original); M.P.E.P. §706.03. It is well recognized that meeting one stated objective is sufficient to satisfy the "how to use" requirement of Section 112.

More specifically, Applicants have disclosed general *in vivo* methodologies, including exemplary methods and enzymes for removal of terminal galactose residues, as well as provided exemplary recombinant glycoprotein systems, *e.g.*, see WO 97/05771. (See, *e.g.*, page 3-4 of the specification). Further, the removal of non sialylated O-linked carbohydrates *via* active enzyme was demonstrated in Example 4. As such, it is submitted that the present specification provided more than adequate guidance to one of skill in the art to practice the invention commensurate in scope with the present claims.

Accordingly, for at least these reasons, the enablement rejection under 35 U.S.C. § 112, first paragraph, is traversed, and withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1-13 and 16-18 stand rejected under 35 U.S.C. § 103(a) as alleged unpatentable over WO 98/31826 to Paulson, *et al.* (hereinafter "Paulson"), Shoenberger, *et al. FEBS* 314; 430-434 (1992) (hereinafter, "Shoenberger"), Wolf, *et al.*, *Protein expression and purification*, 22; 414-421 (2001) (hereinafter, "Wolf"), in view of WO 92/03149 to Glaser, *et al.* (hereinafter "Glaser"). This rejection is respectfully traversed for at least the reasons which follow.

Independent claim 1 is directed to C1 inhibitor, which plasma circulatory half-life has been changed by modification of an O-linked carbohydrate. As acknowledged by the Examiner, Paulson fails to specifically teach C1 inhibitors, or the importance of O-glycosylation. However, in support of the rejection, the Examiner asserts that it would have been obvious "to incorporate into compositions and methods of C1 inhibitor preparations for therapeutic purposes to incorporate sialylation of the recombinantly produced C1 inhibitor to increase its half-life in plasma circulation and use it for therapeutic purposes." Applicants respectfully traverse.

Paulson discloses the *in vitro* sialylation of recombinant glycoproteins. However, as acknowledged by the Examiner, Paulson is silent about the importance of O-linked carbohydrate glycosylation for plasma half-life. Furthermore, C1 inhibitors are not mentioned at all in the cited reference as a potential recombinant glycoprotein. However, the Examiner relies on various aspects of Shoenberger, Wolf, and Glaser to teach C1 inhibitors, characteristic glycosylations, and their various uses. Again, there is no express teaching in any of Shoenberger, Wolf nor Glaser of the importance of O-linked carbohydrates and plasma circulatory half-life.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. The teaching or suggestion to make the claimed combination must be found in the prior art, and not be based on applicant's disclosure. *See* M.P.E.P. §§ 2143.01 and 2143.03.

It is submitted that one of skill in the art would not look to combine the teachings of cited references in the manner suggested. Paulson is directed to methods for *in vitro* sialylation of saccharide groups, preferably of N-linked carbohydrates, of recombinant glycoproteins. Contrary to this, Shoenberger relates to an *in vitro* desialylated C1 inhibitor, and studied its interactions with lectin. It is submitted that one of skill in the art would not look to apply the sialylation methodologies of Paulson to the desialylation methodologies of Shoenberger, or vice-versa. Wolf discloses various aspects of glycosylation patterns of native and recombinant C1 inhibitors, and their relevance to certain disease states. In this regard, it is submitted that one of skill would not look to apply the *in vitro* sialylation methodologies of Paulson to the recombinant glycosylation studies of Wolf.

Finally, Glaser discloses thrombomodulin analogs having modified O-linked glycosylation patterns, and that such analogs can be used for treating thrombotic disease. The O-linked glycosylation patterns may be modified, *e.g.*, enzymatically to remove sulfate substituents (*e.g.*, glycosaminoglycan carbohydrates, see, page 25-26). The analogs are disclosed to have a native ability to inactivate thrombin-mediated activation of protein C and a reduced ability to

inactivate thrombin-mediated conversion of fibrinogen to fibrin. However, it is submitted that one of skill would not look to combine the sialylation methodologies of Paulson with the methodologies disclosed for the modification of the thrombomodulin analogs, *e.g.*, the removal of glycosaminoglycan carbohydrates.

In sum, whatever else the cited references may disclose, as discussed above, it is submitted that one of skill would not look to combine the teachings of Paulson, Shoenberger, Wolf, nor Glaser as suggested. For at least these reasons, this rejection is respectfully traversed and withdrawal of this rejection is respectfully requested.

Nonetheless, even assuming *arguendo*, that one of skill would look to combine the teachings of the cited references, none of the references specifically recognize the importance of O-linked carbohydrates to the plasma circulatory half-life of C1 inhibitors. As such, whatever else the cited references may disclose, taken either separately or in combination, they do not teach or suggest each and every limitation of independent claim 1. For at least this additional reason, this rejection is respectfully traversed and withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,

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